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REVIEW

Systematic review of the cost effectiveness of prophylactic treatments in the prevention of gastropathy in patients with rheumatoid arthritis or osteoarthritis taking non-steroidal anti-inflammatory drugs

Hiske E M van Dieten, Ingeborg B C Korthals-de Bos, Maurits W van Tulder, Willem F Lems, Ben A C Dijkmans, Maarten Boers

Abstract

A systematic review on the cost effectiveness of prophylactic treatments of non-steroidal anti-inflammatory drug (NSAID) induced gastropathy in patients with osteoarthritis or rheumatoid arthritis was conducted. Two reviewers conducted the literature search and the review. Both full and partial economic evaluations published in English, Dutch, or German were included. The criteria list published in the textbook of Drummond was used to determine the quality of the economic evaluations. The methodological quality of three randomised controlled trials (RCTs) in which the economic evaluations obtained probability estimates of NSAID induced gastropathy and adverse events was assessed by a list of internal validity criteria. The conclusions were based on a rating system consisting of four levels of evidence.

Ten economic evaluations were included; three were based on RCTs. All evaluations studied misoprostol as prophylactic treatment: in one evaluation misoprostol was studied as a fixed component in a combination with diclofenac (Arthrotec). All economic evaluations comprised analytical studies containing a decision tree. The three trials were of high methodological quality. Nine economic evaluations were considered high quality and one economic evaluation was considered of low methodological quality. There is strong evidence (level "A") that the use of misoprostol for the prevention of NSAID induced gastropathy is cost effective, and limited evidence (level "C") that the use of Arthrotec is cost effective. Although the levels of evidence used in this review are arbitrary, it is believed that a qualitative analysis is useful: quantitative analyses in this field are hampered by the heterogeneity of economic evaluations. Existing criteria to evaluate the methodological quality of economic evaluations may need refinement for use in systematic reviews.

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Arthritis (rheumatoid arthritis and osteoarthritis) is a common condition and the prevalence of rheumatoid arthritis increases with age to 2% for men and 5% for women over age 55, respectively. The prevalence of osteoarthritis increases from 4% at younger age to 85% over age 75.[1]

Patients with rheumatoid arthritis or osteoarthritis frequently use non-steroidal anti-inflammatory drugs (NSAIDs) for treatment of their arthritis.[2] With the prevalence of arthritis, the prevalence of NSAID use increases with advancing age: about half of all NSAID prescriptions are for patients aged 60 or older.[3]

Although NSAIDs are generally well tolerated, adverse gastrointestinal events occur in a small but important percentage of patients. NSAIDs may cause adverse events ranging in severity from asymptomatic mucosal damage, abdominal pain, heartburn, and dyspepsia to serious complications, such as haemorrhages and perforated ulcers, requiring admission to

hospital. The prevalence of mild adverse events ranges from 5% to 50% for patients treated with NSAIDs. More severe adverse events are less common and have an annual incidence of 1–2%. Because patients with arthritis who frequently use NSAIDs often have other risk factors (advanced age, high doses of NSAIDs, presence of comorbid conditions, previous ulcer), this patient group is particularly at risk of gastrointestinal complications.[4 5] Previous research has shown that 5.4% of patients with NSAID induced adverse events are admitted to hospital.[6] The costs of treating these adverse events are high and include costs of drugs, admission to hospital, and doctor's fees.

Therefore, it is important to have cost effective prophylactic treatments that decrease the incidence of adverse events. In the past decade many economic evaluations on the cost effectiveness of such treatments have been conducted. The conclusions of these evaluations are not consistent, ranging from cost saving and cost effective to costly. Several reviews have summarised the literature, but a systematic approach, including assessment of the methodological quality of the economic evaluations, was not included in these reviews.[7–10]

This article presents a systematic review of the cost effectiveness of prophylactic treatments in the prevention of gastropathy in patients with rheumatoid arthritis or osteoarthritis taking NSAIDs.

This review aimed at evaluating the cost effectiveness of prophylactic treatments to prevent gastropathy by reviewing and assessing the results and methodological quality of economic evaluations.

Methods

LITERATURE SEARCH

Two reviewers (HvD and IK) together identified all relevant studies by searching several electronic databases—namely, Medline (1966 to November 1999), Embase (1988 to September 1998), the NHS Economic Evaluation Database from the University of York, and the Cochrane Library, 1999, issue 1. Keywords used were "non-steroidal anti-inflammatory agents", "rheumatoid arthritis", "osteoarthritis", "costs", "cost analysis", "cost-benefit analysis", "digestive system diseases", "gastritis", "misoprostol", "stomach ulcer", "peptic ulcer perforation", "omeprazole" and "proton pump inhibitor". No further text words were used to identify economic evaluations.

Furthermore, references given in relevant identified publications and reviews were screened. After reviewing the abstract or, in cases where there was any doubt, a copy of the full article, economic evaluations were included in the review if (*a*) the study contained a full or partial economic evaluation, (*b*) the subjects of study were patients with osteoarthritis or rheumatoid arthritis taking NSAIDs, and (*c*) the study assessed any type of prophylactic treatment for NSAID induced gastropathy. The decision on the inclusion of the studies found in the literature search was not blinded, because the two reviewers were unfamiliar with the literature in the field of rheumatic diseases. For practical reasons, only economic evaluations published in English, Dutch, or German were included.

METHODOLOGICAL QUALITY ASSESSMENT

Economic evaluations may be conducted alongside randomised clinical trials (RCTs), but may also consist of a decision analysis. The methodological quality assessment in this review was, therefore, divided into two parts.

Firstly, the quality of the economic evaluations was assessed independently by two reviewers (HvD and IK) with the "checklist for assessing economic evaluations" published by Drummond *et al*[11] (table 1).

Items could be scored as positive, negative, or unclear. Economic evaluations that scored 50% or more of the items positive were defined as studies of high methodological quality, whereas less than 50% was considered low methodological quality.

Secondly, the same two reviewers independently assessed the methodological quality of the original RCTs. Only items related to the internal validity of RCTs, using a criteria list which has been recommended and used by the Cochrane Back Review Group for trials in the field of musculoskeletal disorders,[12] were used (table 2).

Items could be scored as positive, negative, or unclear. RCTs that fulfilled 50% or more of the internal validity items were considered of high methodological quality. RCTs that fulfilled fewer then 50% of the items positive were considered low quality. Disagreements between the reviewers were solved by consensus.

ANALYSIS

The results of the economic evaluations were not statistically pooled, for two reasons:

1 The economic evaluations were conducted in different countries with different healthcare systems. These differences include differences in practice variations, financial incentives, etc which can lead to situations where intervention X is cost effective in country A and costly in country B.[10]
2 The assumptions used in the economic evaluations varied widely.

Instead, a qualitative analysis was conducted with a modified version of a rating system used in the Cochrane Back Review Group. The rating system consisted of four levels of scientific evidence.[12]

1 *Strong evidence* provided by generally consistent findings in multiple high quality economic evaluations based on high quality RCTs or a meta-analysis.
2 *Moderate evidence* provided by generally consistent findings in multiple high quality economic evaluations based on low quality RCTs or observational studies
3 *Limited evidence* provided by generally consistent findings in low quality economic evaluations.
4 *Conflicting evidence*: inconsistent findings.

SENSITIVITY ANALYSIS

In a sensitivity analysis the influence of the threshold for high methodological quality of

Table 1 Criteria list for the quality assessment of economic evaluations[11]: each scored as positive, negative or unclear

Items	*Ref 13*	*Ref 14*	*Refs 15, 16*	*Ref 17*	*Ref 18*	*Ref 19*	*Ref 20*	*Ref 21*	*Ref 22*	*Ref 23*
1. Was a well defined question posed in answerable form?	?	+	−	+	−	+	+	+	+	+
1.1 Did the study examine both costs and effects?	+	+	+	+	−	+	+	+	+	+
1.2 Did the study include comparison of alternatives?	+	+	+	+	+	+	+	+	+	+
1.3 Was a viewpoint for the analysis stated?	+	−	−	+	−	+	−	−	+	−
2. Was a comprehensive description of the alternatives given?	+	+	+	+	+	+	+	+	+	+
2.1 Were any important alternatives omitted?	+	+	+	+	+	+	+	+	+	+
2.2 Was a do-nothing alternative considered?	+	+	+	+	+	+	+	+	+	+
3. Was the effectiveness of the programmes established?	+	+	?	+	+	+	+	?	+	+
3.1 Was this done through a randomised, controlled clinical trial?	+	−	−	+	?	+	+	+	+	+
3.2 Was effectiveness established through an overview of clinical studies?	−	+	−	−	+	−	−	−	−	−
3.3 Were observational data or assumptions used to establish effectiveness?	+	+	+	+	+	+	+	+	+	+
4. Were all the important and relevant costs and consequences identified?	+	+	−	+	?	+	+	+	+	+
4.1 Was the range wide enough for the research question at hand?	+	+	+	+	+	+	+	+	+	+
4.2 Did it cover all relevant viewpoints?	?	−	−	−	?	−	+	−	?	−
4.3 Were capital costs, as well as operating costs, included?	−	−	?	+	−	−	+	+	+	?
5. Were costs and consequences measured accurately in appropriate physical units?	+	+	+	+	+	+	+	+	+	+
5.1 Were any of the identified items omitted from measurement?	+	−	+	+	−	?	−	+	+	+
5.2 Were there any special circumstances that made measurement difficult?	+	−	+	+	−	−	−	−	−	−
6. Were costs and consequences valued credibly?	+	+	?	+	+	+	+	+	+	?
6.1 Were the sources of all values clearly identified?	+	−	+	+	+	+	+	+	+	−
6.2 Were market values employed for changes in resources gained or depleted?	−	−	−	−	−	−	+	+	?	−
6.3 Were adjustments made to approximate market values?	?	−	?	−	−	−	?	+	−	+
6.4 Was the valuation of consequences appropriate for the question posed?	−	+	+	+	−	−	+	+	+	+
7. Were costs and consequences adjusted for differential timing?	−	?	−	−	−	−	−	−	−	−
7.1 Were costs and consequences discounted?	−	−	−	−	−	−	−	−	−	−
7.2 Was any justification given for the discount rate used?	−	−	−	−	−	−	−	−	−	−
8. Was an incremental analysis performed?	−	+	+	+	+	−	−	−	+	−
8.1 Were the additional costs compared with the additional effects?	−	+	+	+	+	−	−	−	+	−
9. Was allowance made for uncertainty in the estimates?	+	+	+	+	+	+	+	+	+	+
9.1 Were appropriate statistical analyses performed?	+	+	+	+	+	+	+	+	+	+
9.2 Was justification provided for the ranges of values?	+	+	+	+	+	+	+	−	−	+
9.3 Were study results sensitive to changes in the values?	?	+	+	+	−	+	+	+	−	+
10. Did the study results include all issues of concern to users?	+	+	?	+	−	−	?	−	+	−
10.1 Were the conclusions of the analysis based on some overall index or ratio?	+	+	+	+	−	−	+	−	+	−
10.2 Were the results compared with those of others?	−	+	+	+	−	−	+	−	+	+
10.3 Did the study discuss the generalisability of the results?	+	+	+	+	+	+	+	+	+	−
10.4 Did the study take account of other important factors?	+	+	−	−	−	?	−	−	−	−
10.5 Did the study discuss issues of implementation?	−	−	−	+	−	−	−	−	−	−
% Positive	61	66	55	79	45	53	66	58	68	53

economic evaluations and RCTs was evaluated by varying the cut off point (that is, using 60% or 70% as a threshold for high methodological quality). The influence on the methodological quality of the items that were scored as "unclear" was evaluated by assuming that an unclear item was scored positive (best-case analysis).

Results

LITERATURE SEARCH

We identified 396 citations in Medline and 248 in Embase. After screening the abstracts and, if necessary, full articles, we reached agreement on the inclusion of 10 economic evaluations.[13–23] All economic evaluations were found in Medline, six were also found in Embase, and three economic evaluations were also found with the use of the NHS database. Nine studies were published in English and one in German.

All evaluations studied misoprostol as prophylactic treatment. In one evaluation misoprostol was studied as a fixed component in combination with diclofenac (Arthrotec).

Table 2 Criteria list for assessing the methodological quality of (randomised) clinical trials[12]: each scored as positive, negative, or unclear

Items	*Agrawal et al[24]*	*Graham et al[25]*	*Silverstein et al[26]*
1. Concealment of treatment allocation			
1a. Adequate allocation concealment	−	−	+
1b. Generation of the allocation sequence	−	−	+
2. Similarity of baseline characteristics	+	+	+
3. Blinding of outcome assessor	+	?	+
4. Blinding of patients	−	+	+
5. Blinding of care provider	−	?	+
6. Identical timing of outcome assessment	+	+	?
7. Withdrawals and dropouts			
7a. During intervention period	+	+	−
7b. During follow up period	+	+	−
8. Adherence to interventions (compliance)	−	−	?
9. Co-interventions	?	−	+
10. Intention to treat analysis	+	+	?
% Positive	50	50	58

ECONOMIC EVALUATIONS

All economic evaluations included in this review were analytical decision studies containing a decision tree. The probability estimates of NSAID induced gastropathy and adverse events of prophylactic treatment in the economic evaluations were derived from either a previously conducted RCT, a meta-analysis, an observational study, or selected literature (combination of RCTs and/or observational studies) and assigned to the change nodes in the decision trees. The decision trees used in the economic evaluations were basically similar. They all started with a decision node for the different prophylactic treatments. The decision trees contained branches with change nodes reflecting the

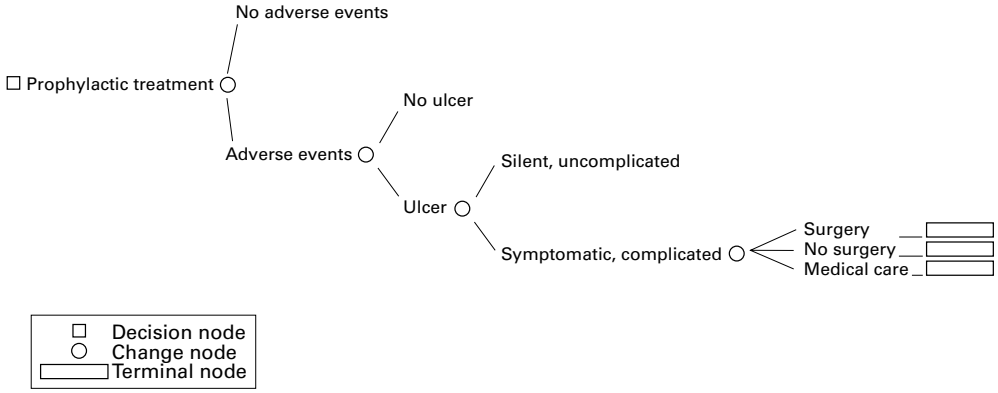

Figure 1 Branches in the decision tree.

probabilities of adverse events during prophylactic treatment. Figure 1 shows the structure of all branches.

METHODOLOGICAL QUALITY OF ECONOMIC EVALUATIONS

Applying a cut off point of ⩾50% positive items resulted in nine high quality evaluations.[13–17 19–23] Only one evaluation was of low methodological quality[18] (table 1).

The viewpoint of the evaluation (item 1.3) was stated in only four evaluations.[13 17 19 22] The viewpoints used in these four evaluations were a societal viewpoint,[13 19] a viewpoint of hospital based services of the provincial healthcare plan,[17] and the provincial healthcare plan.[22] The viewpoint of the evaluation has influence on the costs included in an economic evaluation and the type of outcomes measured.[12] Seven economic evaluations[13 17 19–23]derived data on the effectiveness of prophylactic treatments from RCTs.[24–26] Subitems 3.3 on the use of observational data and 4.1 on the range of costs and consequences were always scored positive. Capital costs and operating costs (item 4.3) were incorporated in four studies,[17 20–22] while five studies omitted these costs and in two studies it was unclear whether these costs were incorporated or not.[15 16 23] Three evaluations[13 15–17] accounted for special circumstances (item 5.2), such as shared operating rooms or overhead costs, the others did not. Only two economic evaluations[20 21] used cost prices instead of market prices (item 6.2), and for one evaluation[22] it was unclear whether cost prices or market prices were used. Neither one of the evaluations adjusted cost and consequences for differential timing. An incremental analysis of costs and consequences (item 8) was conducted in five evaluations.[14–18 22] Six economic evaluations[13–17 20 22] presented their results as cost effectiveness ratios (item 10.1). In six evaluations[14–17 20 22 23] the results of the evaluation were compared with those of other evaluations (item 10.2). Only one of the evaluations[17] discussed implementation (subitem 10.5). This may be due to the fact that the treatment of patients with rheumatoid arthritis or osteoarthritis with some kind of gastroprotection is already implemented in many healthcare systems. Therefore, the implementation of the results of the economic evaluations will not require great effort or will not lead to major changes within healthcare systems.

The 10 economic evaluations were different in several aspects. Table 3 shows the most striking differences.

Three economic evaluations[13 20 21] stated that the use of misoprostol as a prophylactic treatment was cost effective. The economic evaluation of Carrin and Torfs[13] resulted in cost savings ranging from $78 for widows, orphans, pensioners, and invalids and $84 for employees in university hospitals and from $74 to $79 in general hospitals respectively. Lives saved were slightly above 14 per 10 000 in university hospitals and 14.7 in general hospitals. The analytical decision study by Jönsson and Haglund[20] yielded $175 for each patient treated with misoprostol compared with $208 for each patient with no prophylaxis. Knill-Jones *et al*[21] showed that $11 was saved for each case treated with misoprostol over three months in Scotland and $16 in England.

Goldstein concluded that the use of a combination of diclofenac and misoprostol (Arthrotec) was cost effective compared with the use of regular NSAIDs in the prevention of NSAID induced gastropathy.[18] A cost/patient ratio of $1153 for all NSAID regimens and $939 for Arthrotec regimens was presented.

Four economic evaluations[14 17 19 22] stated that the use of misoprostol as a prophylactic treatment was cost effective under certain conditions. These conditions included, for example, the ulcer rate, admission to hospital rate, compliance, patient group, and drug prices. Prophylactic treatments were more cost effective if the ulcer rate and admission to hospital rate were high and the price of the prophylactic pharmaceutical was low.

The economic evaluation conducted by Schwarz[23] reported only on costs.

One economic evaluation[15 16] conducted a cost-utility analysis and concluded that the use of misoprostol costs more and provides no additional quality of life than no prophylaxis.

The overall conclusion, however, was that these economic evaluations clearly showed that the use of prophylactic treatments (misoprostol) for the prevention of gastropathy is cost effective.

Table 3 Study characteristics

Study characteristics:	*Ref 13*	*Ref 14*	*Refs 15, 16*	*Ref 17*	*Ref 18*	*Ref 19*	*Ref 20*	*Ref 21*	*Ref 22*	*Ref 23*
Patients										
Osteoarthritis	x			x		x	x	x		
Rheumatoid arthritis		x	x		x				x	x
Treatment										
Misoprostol	x	x	x	x	x	x	x	x	x	x
Placebo	x	x	x	x	x	x	x	x	x	x
H_2 receptor antagonist					x					
Misoprostol/diclofenac					x					
Study design										
Meta-analysis			x	x						x
RCT	x			x		x	x	x	x	x
Cohort study						x				
Population survey								x		
Selected literature		x			x					
Costs										
* *Direct costs:*										
Admission to hospital	x	x	x	x	x	x	x	x	x	x
Ambulatory care	x	x	x	x		x	x	x	x	x
Drug treatment (prophylaxis)	x	x	x	x	x	x	x	x	x	x
Treatment of adverse events				x					x	
Doctor's visit	x	x			x			x		
* *Indirect costs*							x			
Primary outcome										
Cost/lives saved	x	x								
Cost/adverse events averted				x					x	
Cost/QALY†			x							
Cost/patient					x		x	x		x
Cost only						x				
Misoprostol compared with placebo:										
Cost effective	x				a*		x	x		
Conditionally cost effective		x		x		x			x	
Cost only										x
Costly			x							

*Arthrotec.
†QALY = quality adjusted life year.

METHODOLOGICAL QUALITY OF (RANDOMISED) CLINICAL TRIALS

From three RCTs probability estimates of NSAID induced gastropathy and adverse events were derived.[24–26] The other economic evaluations derived their probability estimates from a meta-analysis,[27] a cohort study,[28] or selected literature. Table 2 shows the results of the consensus on the methodological quality assessment of these RCTs. Previous research has shown that items dealing with randomisation, blinding, and dropouts, in particular, might be associated with bias.[29]

All three RCTs were considered to be high quality, according to our definition. The trial conducted by Silverstein *et al*[26] was a double blinded, randomised clinical trial in which 8843 patients participated (mean age 67, 6–70% women, 83% white) and with only a few dropouts. The other two trials[24 25] were single blinded, had more than 20% dropouts, and included data on 421 patients (mean age 58.9, 65% women, 83% white) and 356 patients (mean age 60.1, 56% women, 89% white) respectively.

In the RCT conducted by Silverstein,[26] in contrast with the RCTs conducted by Agrawal[24] and Graham,[25] the rates of major healthcare resource use were low, and probably reflect more closely the real world than the high rates estimated in the other two trials.

There was no evidence of a relation between the quality of the RCTs and the quality of economic evaluations because all RCTs were of high methodological quality. Nevertheless, all high quality economic evaluations derived their probability estimates from RCTs or meta-analyses and not from selected literature or cohort studies.

COST EFFECTIVENESS

Nine economic evaluations, eight full and one partial,[23] compared prophylactic treatment with misoprostol with placebo. One full economic evaluation[18] compared Arthrotec with NSAID + misoprostol, NSAID + H_2 receptor antagonists, and NSAIDs alone.

Three high quality economic evaluations[13 20 21] (level of evidence "A") concluded that the use of misoprostol as a prophylactic treatment for the prevention of gastropathy was cost effective. Three high quality economic evaluations[17 19 22] (level of evidence "A") and one evaluation[14] of moderate quality (level of evidence "B") stated that the use of misoprostol was cost effective, though under certain conditions. One partial high quality[23] economic evaluation reported only on the costs of treatment with a pharmaceutical prophylaxis. Gabriel stated that prophylactic treatment with misoprostol is costly, unless it is used in high risk NSAID users.[15 16] The distinction in this article between prophylaxis for elderly NSAID users and prophylaxis for all NSAID users explains the different result of this economic evaluation compared with the others.

Goldstein concluded that the use of Arthrotec generates fewer costs than NSAID + misoprostol, NSAID + H_2 receptor antagonists, and NSAIDs alone (level of evidence "C").[18]

The economic evaluation conducted by Maetzel *et al*[22] was the only evaluation that derived the probability estimates of NSAID induced gastropathy and adverse events of prophylactic treatments from the RCT of Silverstein.[26] This RCT reflects more the real life effectiveness of prophylactic treatment than the RCTs conducted by Agrawal[24] and Graham.[25] Therefore, the economic evaluation of Maetzel is the best approach to the cost

effectiveness of the use of prophylactic treatments in daily practice.

The overall conclusion is that there is strong evidence (level "A") that the use of misoprostol is cost effective as prophylactic treatment in the prevention of gastropathy in patients with arthritis.

SENSITIVITY ANALYSIS

Varying the cut off point between ⩾60% and ⩾70% positive items resulted in five[13 14 17 20 21] and one[17] high quality economic evaluation respectively (table 1).

A cut off point of ⩾60% positive items resulted in four evaluations on the cost effectiveness of misoprostol[13 17 20 22] with level of evidence "A". A cut off point of ⩾70% positive items yielded one evaluation[17] with level of evidence "A". Varying the cut off point, however, did not change the overall conclusion of this review.

Changing the "unclear" items to "positive" items in the methodological quality assessment also resulted in the same conclusions.

Discussion

There was strong evidence (level "A") that misoprostol is cost effective in the prevention of NSAID induced gastropathy. This overall conclusion may be biased for two reasons. Firstly, it is possible that economic evaluations with a negative outcome are not published and, therefore, not included in this review. Secondly, it might be that the probability estimates of NSAID induced gastropathy and adverse events used in the economic evaluations are based on patients with a high risk of developing gastrointestinal complications, which makes an intervention more cost effective for those patients than for patients with moderate risk.

The slightly different conclusions reached by the economic evaluations may be explained by the different assumptions that were used.

Goldstein,[18] like Plosker and Lamb,[29] concluded that the use of Arthrotec as prophylaxis for gastropathy was cost effective compared with the use of NSAID + misoprostol, NSAID + H_2 receptor antagonists, or NSAIDs alone. However, this evaluation was of poor methodological quality.

Our systematic review is methodologically different from earlier conducted reviews[7–10] on this subject for several reasons.

Firstly, this is the first systematic review on this subject that contains a systematically performed literature search conducted by two researchers, according to the most up to date methodology.[30 31] The previously conducted reviews on this subject only searched Medline,[7 8] or the database in which the economic evaluations were found was not mentioned.[9 10] The number of economic evaluations included in these reviews ranged from five to eight, whereas we identified 10 economic evaluations. After correction for the date of publication, nine of the 10 economic evaluations included in this review were published at the time of publication of the above mentioned reviews.

Secondly, the methodological quality of the RCTs from which the probability estimates of NSAID induced gastropathy and adverse events were derived was assessed. This is necessary because the quality of an economic evaluation of medical technologies may depend upon the quality of the assessment of the clinical effectiveness of these technologies.[32] High quality RCTs are more likely to provide valid estimates and, consequently, economic evaluations using data from these RCTs are also less likely to provide biased results.

Thirdly, we used the criteria list of Drummond *et al*[11] to assess the methodological quality of economic evaluations. Not every item or subitem in this criteria list was suitable for quality assessment of the economic evaluations included in this review. Subitem 1.2 and item 2 and its subitems both referred to the alternatives included in the evaluation (table 1). Subitems 1.3 and 4.2 were both questions about the viewpoint of the evaluation. The scoring of item 7 and its subitems on discounting of costs and consequences depends on the time horizon of the study. It is unclear which items in the criteria list of Drummond are related to the internal validity of an economic evaluation, which indicates the possibility of bias in the results of a study. Therefore, to assess the quality of economic evaluations, a criteria list like the list with items related to the internal validity of RCTs[31] has to be developed.

The conclusions of this review are slightly different from those of earlier conducted reviews. Stucki stated that "the absence of firm data on the rate of NSAID induced gastric ulcers reduced by misoprostol makes it impossible to conclude whether it is cost effective in patients with chronic arthritis who use NSAIDs".[7] In the review published by Gabriel[9] the authors came to the conclusion that "the widespread use of misoprostol prophylaxis not only has important economic consequences, but has important consequences for quality of life. More research is needed to address the clinical trade-offs between cost and quality of life that are inherent in the use of NSAIDs".

All evaluations included in this review were decision analytical studies. As described above, some items and subitems of the criteria list of Drummond were less appropriate for the quality assessment of these evaluations. If items 1.2, 3.3, 4.2, and 7 had not been incorporated in the quality assessment of the economic evaluations, the proportion of positively scored items of all evaluations would have been higher.

All these studies contain decision trees implying modulation and simulation of probabilities on a fictive population. There are several simulation models, such as the Markov and Monte Carlo models. However, only two economic evaluations mentioned the simulation model used.[15 16 18]

There is evidence that some patients experience substantial losses in quality of life because of adverse events of prophylactic drugs.[9] However, only one economic evaluation included quality of life and conducted a cost-utility analysis.[15 16] Future economic evaluations should include such an analysis because it enables comparison of the cost-utility between different medical technologies.

The time horizons of the economic evaluations were relatively short, considering that NSAID induced gastropathy may occur at any time in the long term treatment of arthritis. The cause of those short time horizons is that the follow up periods used in the RCTs were used as the time horizons in the economic evaluations.

The levels of evidence used in this review were arbitrary. We used a modified version of a Cochrane rating system that is similar to the rating system used by the Cochrane Back Review Group. Other levels of evidence or rating systems are available. The choice is arbitrary. The methodology of qualitative analysis of systematic reviews of economic evaluations should be further developed. However, we do believe that a qualitative analysis using levels of evidence is a good alternative in systematic reviews when a quantitative analysis (meta-analysis) is either not possible or not useful in cases where the study groups, interventions, and outcomes of studies are too heterogeneous.

To summarise, the results of this review confirmed that there is strong evidence that it is cost effective to prescribe misoprostol as prophylactic treatment in arthritic patients taking NSAIDs in daily clinical practice.

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